REMARKS

Claims 12-17 are pending and subject to a restriction requirement. Claim 16 is withdrawn. Claims 12, 13, and 17 have been amended. Applicant kindly requests reconsideration of all the pending claims.

Claim Objections

Claims 12 and 13 are objected because of a missing phrase and typographical error. These formal requirements have been corrected in the present amendment; therefore Applicant respectfully requests withdrawal of this objection.

Claim Rejections Under Section 112, Second Paragraph

Claims 12 and 13 are rejected under Section 112, second paragraph as being indefinite in the recitation of terms and phrases: derivative, derived from, is capable of inserting in lipids bylayers. Applicant has removed these terms and phrases from the present claims.

Claim Rejections Under Section 112, First Paragraph

Claims 12, 13 and 15 have been rejected under section 112, first paragraph as not being enabled for all the listed diseases but for treatment of insulin resistance. Applicant has amended the claims to list treatment of insulin resistance, overweight and obesity. Applicant submits that the claims are sufficiently enabled for these listed diseases for the reasons stated below.

Applicants have demonstrated in the examples provided in the specification, that the listed compounds and genus compounds are effective in decreasing the accumulation of the glycosphingolipid GM3 in the cells. Glucosylceramide synthesis is required and rate limiting for synthesis of GM3 in cells. GM3 is known to accumulate as rafts in the lipid bylayer of the cells and decrease the function of insulin. One of the hallmarks of obesity is the accumulation of GM3 in the lipid bylayers, and, as shown in the attached abstract published from the present inventor (see van Eijk et al), applicant has demonstrated that by decreasing the production of GM3 in the cell one can reverse the course of insulin resistance in obese mice and minimize the presence of macrophage that are indicative of inflammatory response. Thus applicant has demonstrated a clinical benefit of treating obese patients. It has now been well accepted that being overweigh increase the risk of developing insulin resistance later in life and is associated with low grade inflammation (see abstract of Antuna-Puente et al. and Costarelli et al.). Thus it

would be within a person skilled in the art to reasonably expect a clinical benefit by treating a patient being overweight with the compounds of the invention.. Therefore applicant submits that the present claims are sufficiently enabled in view of the state of knowledge in the art. Thus, applicant respectfully requests withdrawal of this rejection.

Claim Rejections Under Section 103(a)

The claims are rejected under section 103 (a) as being allegedly obvious over a combination of prior arts: Aerts (US6,177,447), Mastumoto and DeAlmeida. Applicant respectfully disagrees as the combination of references does not teach or suggest the invention as a whole.

Applicant's invention is directed to specific deoxynojirimycin compounds, all presenting a large hydrophobic moiety that comprises an apolar polycyclic alcohol containing three or more rings each sharing two or more carbon atoms with another ring. Examples of such compounds listed in the dependent claim 13 provide for such apolar moiety to be adamentanemethanol, cholesterol, β-cholesterol, adamantanol, and 9-hydroxyphenanthrene. These materials have been identified has having a selectively high inhibitory activity (preferably IC50 of below 1 μM) for glucosyl ceramide synthase while having a low inhibitory activity for intestinal sucrase, maltase, and/or lactase (preferably IC50 of above 1 μM) (see specification page 4, lines 13-32, page 15, table 1). Applicant's point of novelty stems from the realization that the activity of glucosylceramide synthase in the plasma membrane plays a role in the synthesis of GM3 which in obese people accumulates in the cells membrane and impairs insulin signaling. Applicant demonstrated that the inhibition of the glucosylceramide synthase leads to a restoration of insulin signaling and thus presents a therapy for insulin resistant in Type 2 diabetes patients as well as people predisposed to developing this disease such as those who are overweight or obese.

Aerts et al. teach the use of substituted deoxynojirimycins for the treatment of Gaucher disease. Gaucher disease results from the accumulation of glycosphingolipids (i.e. glucosylceramide) in the lysosomes of macrophages. Aerts et al. teach that activation of these macrophages is associated to the morbidity of Gaucher disease from the activity of nonlysosomal glucosylceramidase located in the plasma membrane. Glucosylceramidase hydrolyses glucosylceramide releasing ceramide and glucose in the plasma membrane. Ceramide released in

the plasma membrane is involved in the signaling of cytokine secretion of activated macrophage. Aerts et al. disclose substituted deoxynojirimycins that are inhibitors of the glucosylceramidase. Thus, Aerts et al. focus on the ceramide and glucosylceramide pathways in the plasma membrane and not on the interdependence of the glucosylceramide and glucose pathways. In particular Aerts et al. teach or suggest nothing about the negative correlation between the presence of the glycosphingolipids GM3 (a glycosphingolipid derived and downstream from glucosylceramide) in the cells' membrane and the activity of the glucose transporter Glut4. Thus, as the examiner recognizes, Aerts et al. do not teach the use of these substituted deoxynojirimycin for the treatment of insulin resistance, overweight or obesity. A person skilled in the art would not make any connection between these diseases and Gaucher based on the teachings Aerts et al.

Matsumoto does not cure the defects of Aerts et al. and is not a combinable reference. Matsumoto teaches compound having activities at opposite ends of the glucose pathways than the ones presently claimed. Matsumoto is principally interested in developing assays for measuring the inhibitory activity of compounds on the α-glucosidase, an enzyme found in the gut and responsible for the release of glucose from disaccharides and its subsequent absorption from gut into the blood stream. Nothing in Matsumoto teaches or suggests the person skilled in the art to focus on the other aspect of glucose metabolism - its transfer from the blood into the muscle or adipose cells in order to treat insulin resistance. In particular Matsumoto teaches nothing about the negative correlation between the presence of the glycosphingolipids GM3 in the cells' membrane and the activity of the glucose transporter Glut4. In fact it is the present inventor who first proposed such correlation and demonstrated that the use of a glucosylceramide inhibitor would lead to the reduction of GM3 in the cell and thus also at the cell membrane and improved glucose absorption by the cells (see specification from page 1, line 30 to page 3, line 7).

Further, the present inventor is specifically selecting inhibitors of glucosylceramidase that are not active with α-glucosidase or the other maltase and lactase in the gut, to avoid undesirable side effects. Thus a person skilled in the art would not look to Matsumoto to design selective inhibitors of glucosylceramidases. It is the present inventor who recognizes that the lack of selectivity of the Matsumoto compounds leads to undesirable side effects (see specification at page 3, lines 30), and who, trying to increase the selectivity towards the glucosylceramidase in the plasma membrane, hypothesizes that the presence of a large hydrophobic moiety on the

deoxynojirimycin would lead to an improved selectivity see specification at page 5, lines 16-29). Matsumoto compound (1-deoxynojirimycin) lacks that large hydrophobic moiety and also lacks the selectivity as recognized by the current inventor (see specification at page 4, lines 13-32). Thus Matsumoto, does not suggest to a person skilled in the art the adequacy of the compounds of Aerts et al. for the treatment of insulin resistance, overweight and obesity with the improved clinical profile of reduced side effect in the gut.

DeAlmeida also does not cure the deficiencies of Aerts et al or Matsumoto. DeAlmeida teaches the uses of a peptide (Dkk-5) to treat insulin resistance. This peptide stimulates both basal and insulin-stimulated glucose metabolism, i.e. improve glucose intake by the cells. In particular, DeAlmeida suggests that administration of this peptide affects the expression levels of proteins in the insulin-signaling pathway (see page 3, paragraph [0023]). DeAlmeida does not teach or suggest the negative correlation between the presence of the glycosphingolipids GM3 in the cells' membrane and the activity of the glucose transporter Glut4. Further, DeAlmeida does not teach the needs to design small molecules having a large hydrophobic moiety to favor selectivity the inhibitory activity against glucosylceramidase over α-glucosidase, maltase and lactase. Thus a person skilled in the art would not foresee the adequacy of the compounds of Aerts et al. for the treatment of insulin resistance, overweigh and obesity from the teaching of DeAlmeida.

Therefore applicant submits that the combination of references does not teach or suggest the presently claimed invention, and respectfully requests withdrawal of this rejection.

Double Patenting:

Upon a finding of allowable subject matter, Applicant will submit a terminal disclaimer.

Applicant believes it has addressed all rejection set forth in the above-mentioned office action and respectfully requests favorable reconsideration of the instant application.

Respectfully submitted,

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Encl: 3 abstracts